

IMAGING TECHNIQUES

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Imaging of McCune-Albright syndrome using bone single photon emission computed tomography

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Abstract McCune-Albright syndrome is a rare disorder caused by a somatic, constitutively activating mutation in the gene (GNAS1) encoding the subunit of the signal transducing guanine nucleotide binding protein (G protein). The condition is characterized by polyostotic fibrous dysplasia, *cafe-au-lait* pigmentation and multiple endocrine hyperfunction, most commonly gonadotropin-independent precocious puberty in girls. Our patient, a 16-year-old male, with radiologically confirmed polyostotic fibrous dysplasia in cranium, thoracic and pelvic girdles, spine and extremities was studied using planar ^{99m}Tc -hydroxymethyldiphosphonate bone scintigraphy and single photon emission computed tomography. Using bone scintigraphy, an unusually extensive and asymmetric fibrous dysplasia was observed in the cranium, face, ribs, femur, humerus, ulna, tibia and the vertebral column, all on the left side. The whole body scan revealed only a few foci on the right side. Single photon emission computed tomography demonstrated extensive unilateral involvement in the base of the skull, facial bones, maxilla and mandible. All the lesions reached only the midline. These findings formed the basis of further treatment, eg. reconstructive surgery of facial asymmetry.

Conclusion McCune-Albright syndrome should be considered in the differential diagnosis when interpreting extensive unilateral predominance in paediatric bone scans.

Key words McCune-Albright syndrome · Radionuclide imaging · SPECT

Abbreviations MAS McCune-Albright syndrome · SPECT single photon emission computed tomography

Introduction

McCune-Albright syndrome (MAS) is a rare condition characterized by polyostotic fibrous dysplasia, *cafe-au-lait* skin pigmentation and various endocrine hyperfunctions, most commonly precocious puberty [1, 7], which is usually gonadotropin independent. Cushing

syndrome, growth hormone secreting pituitary adenoma, hyperprolactinaemia, nodular toxic goitre, and pheochromocytoma may also occur in affected patients. Of reported cases, 95% have been females. Here we report a rare case of a male patient with MAS displaying multiple skeletal lesions. Bone single photon emission computed tomography (SPECT) was useful in localizing polyostotic lesions.

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Case report

The patient was the first child of a 28-year-old mother and 30-year-old father, both reportedly healthy. He was born by Caesarean section; his birth weight was 3650 g and height 53 cm. His Apgar score was 9 at 1 min. At the age of 5 years he developed pain in the left femur. Radiological findings suspected fibrous dysplasia as a cause of the pain. Consistent with the diagnosis of MAS, *cafe-au-lait* pigmentation was found on the left side of the neck. Serum alkaline phosphatase was also elevated (1119 U/L; reference range 250–750 U/L). Serum testosterone was within the prepubertal range and no clinical signs of puberty were observed; however, the left testis was larger (5.8 mL) than the right one (1.2 mL). LH and FSH were in the low prepubertal range (both as 0.1 IU/L). Serum thyroxine and parathormone levels were normal. He also had a normal cortisol response to ACTH and normal growth hormone and ACTH responses in arginine and insulin provocation tests.

At the age of 6 years he had his first fracture in the left humerus. Six months later he fractured his left femur and had a second fracture in the left humerus. Subsequently he had several bone fractures in the left femur, tibia and humerus, radius and ulna. At the age of 15 years the left tibia, humerus and femur were osteotomised to repair the malformations.

At the time of scintigraphy the patient was 16-years-old and had no neurological symptoms. His pubertal status was Tanner stage P4, G5. At school he was doing well. His major problem was the facial asymmetry and abnormal growth of the extremities on the left side. The left testis (52 mL) was still also larger than the right one (14 mL). All the major findings, i.e. *cafe-au-lait* pigmentation, unilateral macro-orchidism, and polyostotic fibrotic dysplasia were consistent with the diagnosis of MAS.

Bone SPECT was done to localize affected sites before reconstructive plastic surgery for facial asymmetry.

The patient was imaged using a Toshiba GCA-901A/HG gamma camera (Toshiba, Tokyo, Japan) equipped with a low energy high resolution collimator (140 keV; 20% windows). After injecting 740 MBq ^{99m}Tc -hydroxymethyldiphosphonate (Osteoscan, Mallinckrodt BV, Petten, The Netherlands) the whole body was scanned at 125 mm/min using a matrix size 256×1024 .

At 3 h SPECT (360) was performed by collecting 20 s frames with a matrix size 128×128 . Altogether 60 frames were collected with six angular intervals. This made the pixel size $4 \text{ mm} \times 4 \text{ mm}$. The findings were compared with those of plain X-rays and CT of the skull, including 3D reconstruction.

Results

The whole body scintigraphy (Fig. 1A) demonstrated extensive lesions on the left side in the skull, distal humerus, proximal ulna and radius, carpal bones, ribs, scapula, lower thoracic and lumbar spine, ischiadic bone, acetabulum, proximal femur, proximal tibia and ankle. On the right side only a few foci in the femur were observed. Native X-rays were used to demonstrate all the lesions seen on the bone scan. For comparison a lateral view from the left tibia is shown with three major lesions of polyostotic fibrous dysplasia (Fig. 1B). The bone SPECT (Fig. 1C) demonstrated 11–14 sagittal, transaxial and coronal sections. An extensive involvement of the left mandible, maxilla, nasal bone, ethmoid bone, sphenoid bone, vomer, frontal bone, zygomatic bone and arc, temporal bone were seen. Separate foci were observed in the left temporoparietal and occipital regions. The findings on the right side were normal. The 3D CT reconstruction (Fig. 1D) confirmed the remark-

able facial asymmetry due to polyostotic fibrous dysplasia.

Discussion

The molecular basis of MAS has been recently characterized [9]. The condition is caused by a somatic, constitutively activating mutation in the gene (GNAS1) encoding the subunit of the signal transducing guanine binding protein (G protein) that activates adenylyl cyclase [12, 15], which results in increased cyclic adenosine 3',5'-monophosphate production in affected cells. Our study demonstrates scintigraphic findings in this rare condition. In this syndrome, males are very seldom affected. The fibrous dysplasia in our patient was unilaterally distributed, most of the lesions were located on the left side.

GNAS1 activating mutations are not present in all cells of affected patients, not even within affected organs. Mutated cells are distributed in a mosaic pattern, with the greatest number present in the most abnormal areas of affected tissues [12, 14]. These observations have led to the hypothesis that MAS is not a germline mutation rather a postzygotic one [3]. The distribution of affected cells follow embryological lines of ectodermal migration, which explains the unilateral and focal expression of MAS in the bones as well as in many endocrine tissues [3]. Furthermore, the earlier in embryonic development the mutation takes place, the more cells are affected.

Bone SPECT revealed extension into the mid-line in the skull (Fig. 1C). According to Pfeffer et al. [8] the skull (18 out of 22), mandible (11 out of 22), and facial bones (10 out of 22) are very often affected, as in our case. The vertebrae are seldom affected (only 2 out of 22) [8]. Our case demonstrated unilateral uptakes even in the spine, especially in the lumbar region (Fig. 1A). The lumbar uptakes were in the facet joints, and were not degenerative nor stress changes at the site of scoliosis. Symmetric conditions have also been described [13]. In our case the left ankle was also involved, a finding not previously reported [8]. The superior sensitivity of bone scanning over conventional radiology has been shown in studies with a small number of patients [5, 6]. In our case all the lesions could be confirmed by conventional X-ray techniques. MRI will be helpful in selected conditions [4, 13].

Bone SPECT findings have to our knowledge not been reported in the literature. It was very helpful in diagnosis and planning further diagnostic and therapeutic operative procedures by revealing the sites of abnormal growth potential. Abnormal growth potential is associated with high uptake due to increased number of osteoblasts. The 3D CT image (Fig. 1D) can be used for planning of surgical reconstruction, but is unable to locate active osteoblastic sites of fibrous dysplasia seen on SPECT. The craniofacial fibrous dysplasia can demonstrate unusual manifestations and complications; optic nerve compression observed by CT resulting in blindness has been reported [2].

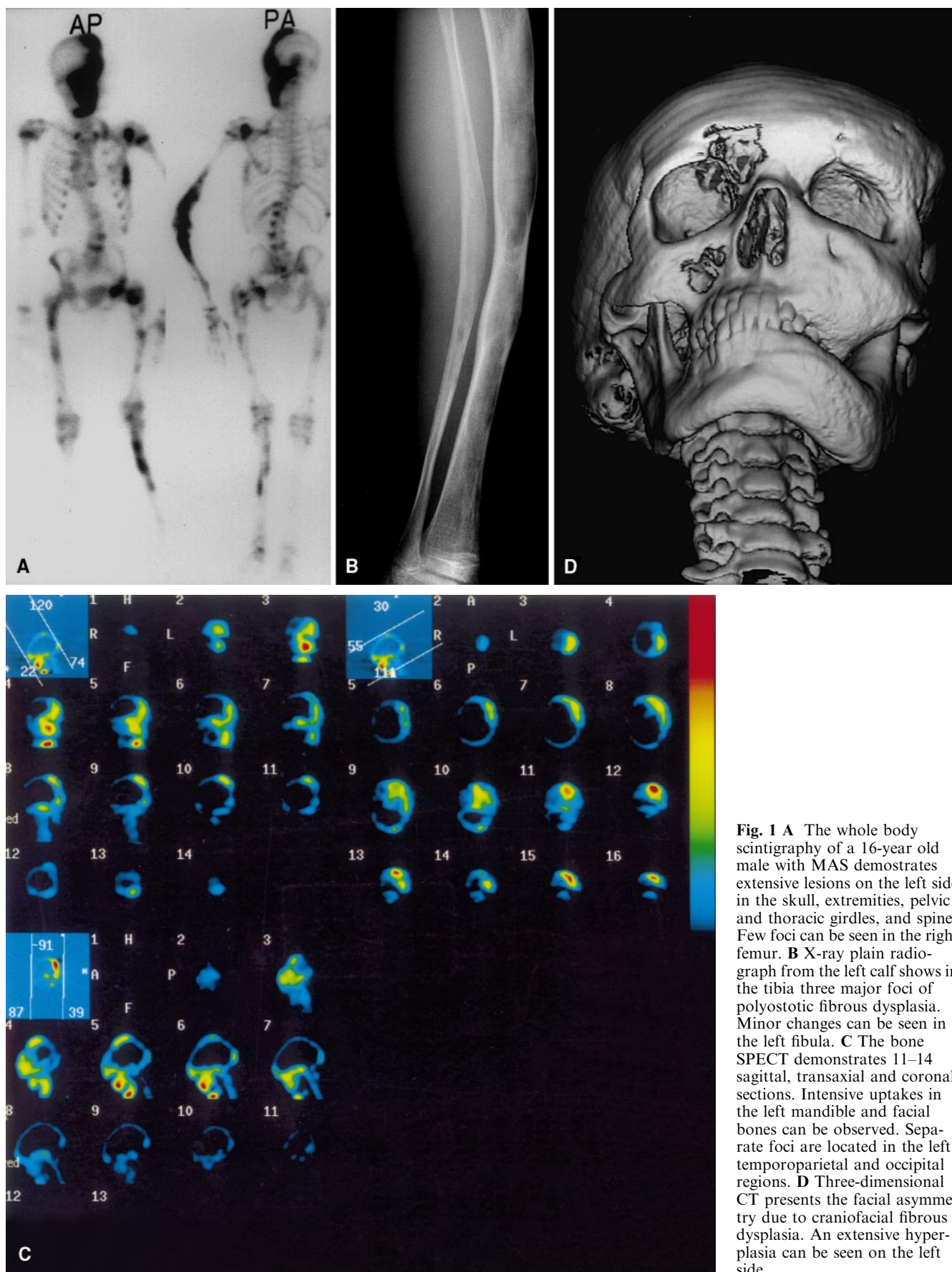


Fig. 1 **A** The whole body scintigraphy of a 16-year old male with MAS demonstrates extensive lesions on the left side in the skull, extremities, pelvic and thoracic girdles, and spine. Few foci can be seen in the right femur. **B** X-ray plain radiograph from the left calf shows in the tibia three major foci of polyostotic fibrous dysplasia. Minor changes can be seen in the left fibula. **C** The bone SPECT demonstrates 11–14 sagittal, transaxial and coronal sections. Intensive uptakes in the left mandible and facial bones can be observed. Separate foci are located in the left temporoparietal and occipital regions. **D** Three-dimensional CT presents the facial asymmetry due to craniofacial fibrous dysplasia. An extensive hyperplasia can be seen on the left side

The biochemical nature of the mono- or polyostotic bone lesions is presently somewhat unclear. The number of osteoclasts in MAS patients has been remarkably increased being approximately 35-fold as compared to control patients [16]. Also, the number of nuclei in osteoclasts of MAS patients was more than double as compared to controls [16]. The osteoclast conditions resemble those of Paget disease, whose pathogenesis is explained with by increased interleukin-6 secretion [10]. Interleukin-6 plays also an essential role in the bone lesions of MAS [16]. In vivo bone scintigraphic findings in this MAS patient were similar to those seen idiopathic fibrous dysplasia and Paget disease. In a large review, 3 out of 158 MAS patients developed osteosarcoma [9]. The differential diagnosis between fibrous dysplasia and osteosarcoma may be obtained by scintigraphy, but is extremely difficult. It is not known whether the osteosarcoma represents a malignant degeneration of fibrous dysplasia. In one MAS case described in the literature the change was demonstrated using plain radiographs of the ilium and proximal femur [11].

At present, when extensive unilateral uptakes in paediatric bone scans are seen, postzygotic germline mutations associated with developmental ectodermal migration have to be considered. Our case representing MAS with activating mutations in the *GNAS1* gene is a good example of extensive unilateral polyostotic disease.

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